REMARKS

I. Status of the Claims. Claims 36-96 are pending. Claims 44-65 and 74-96 have been withdrawn from examination by the Examiner as being directed to non-elected subject matter. Claims 36-43 and 66-73 are under examination. By this Amendment, no new matter has been added to the application.

II. Claim Rejections. The claim rejections set out in the Office Action are summarized and addressed as follows.

(i) Double patenting. Claims 36-43 and 66-73 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over certain claims of co-pending application no. 10/001,245 ("the '245 application").. Applicants confirm that the '245 application has not issued as a patent. Accordingly, Applicants are not required to respond to the instant rejection at this time.

It is noted that the instant application was filed prior to the '245 application. Thus, according to the rules of practice, if the obviousness-type double patenting rejection is the last remaining rejection in the instant application and rejections remain in the '245 application, the obviousness-type double patenting rejection of the instant claims should be withdrawn and the application permitted to issue as a patent without the filing of a terminal disclaimer. *See* MPEP §804.I.B.1.

(ii) Rejection Under 35 U.S.C. §112, first paragraph (written description). Claims 36, 38-43 and 66-73 remain rejected for alleged failure to comply with the written description requirement. The rejection is respectfully traversed, on the grounds that the Examiner has failed to state facts that establish a lack of written description.

The written description requirement "ensure[s] that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as detailed in the patent specification." *Reiffin v. Microsoft Corp.,* 214 F.3d 1342, 1354 (Fed. Cir. 2000); *Univ. of Rochester v. G. D. Searle & Co.,* 358 F.3d 916, 922 (Fed. Cir. 2004) Determination of compliance with the written description requirement of section 112 "is a fact-

based inquiry that will depend on the nature of the invention." *Carnegie Mellon Univ. v. Hoffmann-La Roche, Inc.,* 541 F.3d 1115, 1122 (Fed. Cir. 2008), *citing Enzo Biochem, Inc. v. Gen-Probe Inc.,* 323 F.3d 956, 963 (Fed. Cir. 2002). "The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge." *Capon v. Eshhar,* 418 F.3d 1349, 1357 (Fed. Cir. 2005). "[T]he determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter." *Id.* at 1359. "Such knowledge may change as time progresses." *Carnegie Mellon Univ.,* 541 F.3d at 1122, *citing In re Wallach,* 378 F.3d 1330, 1334 (Fed. Cir. 2004).

The updated USPTO updated patent examiner training materials on the written description requirement ("the New Training Materials," available at http://www.uspto.gov/web/menu/written.pdf) set forth that determination of whether a claim meets the written description requirement "should include" a consideration of ten factors and subfactors. New Training Materials at page 1. Applicants' prior response filed April 30, 2008 ("the April 30 response") included a detailed consideration of the factors set forth in the New Training Materials, including a consideration of actual reduction to practice, the disclosure of drawings or structural chemical formulas, identifying characteristics, e.g., physical properties shared and functional characteristics coupled with a known or disclosed correlation between function and structure, method of making the claimed invention, level of skill and knowledge in the art, and predictability in the art. *See* April 30 response at pages 3-8.

The Examiner has failed to respond substantively to the April 30 response. The Examiner has acknowledged the factors set out in the April 30 response by copying Applicants' analysis into the latest Office Action. *See* pages 7-10. Similarly, in the latest Office Action on pages 5-7, the Examiner has copied and recited each of the limitations set forth respectively in claims 36, 38-43 and 66-73. The Examiner again quotes the respective claim limitations on page 11 of the Office Action. Lengthy and verbatim repetition of claim limitations and Applicants'

argument, however, does not equate with "a fact-based inquiry that [depends] on the nature of the invention" (*Carnegie Mellon Univ.,* 541 F.3d at 1122) that is "applied in the context of the particular invention and the state of the knowledge" (*Capon,* 418 F.3d at 1357). In view of the Examiner's failure to substantively consider Applicants' detailed consideration of the factors that the USPTO acknowledges "should be considered" in determining written description, the Examiner's assertion that the specification fails to provide adequate written description for the claims is mere conclusion, unsupported by facts. Because the written description rejection is by facts, it should be withdrawn.

Moreover, the sole factual assertion by the Examiner is mistaken. The Examiner thus asserts, "[t]here is also no indication in the specification as to how the particular point mutation strategy relates to the claimed functions such that one would know how to change the function by a particular mutation." Office Action at page 12. Contrary to the Examiner's assertion, the specification when read in view of the knowledge in the art provides an abundance of guidance on making the claimed recombinant mutant Bet v 1 allergens.

It was general knowledge in the art at the time the application was filed that allergens with reduced IgE binding could be produced by site-directed mutagenesis. *See* specification and cited references at page 7, line 26, et seq. The specification further discloses that the amino acids available for antibody binding are located on the surface of allergens (*see* specification at page 19, lines 30-36). The functional characteristic of reduced IgE binding flows directly from (i.e., is "coupled with") the known property of IgE epitopes to be present on the surface of allergens, particularly in conserved patches on the allergen surface, and the disclosed and well known correlation that disrupting IgE epitopes will reduce IgE binding. The state of the art was such that it was known, for example, that Bet v 1 allergens include IgE epitopes, that they reside in surface patches, that Bet v 1 proteins from the order Fagales share a high level of identity and exhibit cross reactivity, and that substitution of amino acids on the surface of Bet v 1 allergens could disrupt IgE epitopes and lower IgE binding.

The specification sets forth that:

> The major birch pollen allergen Bet v 1 (SEQ ID NO: 37) shows about 90% amino acid sequence identity with major allergens from pollens of taxonomically related trees, i.e. *Fagales* (or instance hazel and hornbeam) and birch pollen allergic patients often show clinical symptoms of allergic cross-reactivity towards these Bet v 1 homologous proteins.

Specification at page 24, lines 8-14. Based on the level of skill in the art at the time the application was filed, a worker of ordinary skill in the art would have recognized that the high degree of identity among Bet v 1 homologous proteins from the order Fagales and the finding that birch pollen allergic patients exhibited symptoms of allergic cross-reactivity towards these homologous proteins indicates that Bet v 1 homologous proteins from the order Fagales have highly similar primary sequences and three-dimensional structures, indicating that the features that are set forth above and which indicate that the Applicants had possession of the mutant allergens for Bet v 1 proteins from the order Fagales also hold for the broader genus of recombinant mutant allergens of Bet v 1 homologous proteins from the order Fagales. Thus, the specification provides written description for the full scope of recombinant mutant Bet v 1 allergens from the order Fagales. *See* claims 36 and 66.

The specification read in light of the knowledge of the state of the art also provides written description for each of the particular features recited the claims. Thus, the general level of skill and knowledge in the art would readily allow one of ordinary skill in the art to use the known crystal structure of Bet v 1 and/or sequence alignment of Bet v 1 sequences to identify amino acids that have a solvent accessibility of 20% (claims 38 and 68), identify amino acids that are conserved with 70% identity among Bet v 1 allergens from the order Fagales (claims 39 and 69), wherein a conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400Å of the surface of said naturally-occurring Bet v 1 allergen (claims 42 and 72), wherein the solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen is substituted with an amino acid that is not conserved among Bet v 1 homologous

allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen occurs (claims 43 and 73) and wherein said allergens homologous to Bet v 1 have an amino sequence that yields a BLAST probability of less than 0.1 when compared to an amino acid sequence of SEQ ID NO: 37 (claim 67). The specification further provides extensive guidance on tests that can be used to determine with recombinant Bet v 1 allergens have IgE binding reduced by at least 5%, compared to the naturally-occurring Bet v 1 allergen from which it is derived (claims 40 and 70) and wherein average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1 allergen is less than 2Å (claims 41 and 71).

Thus, the Applicants were in possession of the complete subject matter of claims 36, 38-43 and 66-72.

The Examiner, moreover, explicitly contradicts the assertion that there is "no indication in the specification as to how the particular point mutation strategy relates to the claimed functions such that one would know how to change the function by a particular mutation," by stating that "one [can] figure out what allergen mutants are encompassed by the instant recitation and make them." One can figure out "how to change [Bet v 1] function by a particular mutation" because the specification details precisely which amino acids are to be mutated, i.e., solvent-accessible amino acid residues that are conserved among Bet v 1 homologous allergens within the order Fagales (*see* specification at page, 14, line 34 – page 15, line 4), preferably wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400Å of the surface of said naturally-occurring Bet v 1 allergen (specification at page, 15, lines 6-11).

The structure of Bet v 1 was known at the time the application was filed and Bet v 1 allergens are highly conserved. There is no rule that the Applicants provide description of the precise mutant amino acids in the claimed recombinant Bet v 1 mutants. *Falkner,* 448 F.3d at 1366. Applicants are entitled to "flexibility" in how they claim their invention. *Univ. of Rochester,* 358 F.3d 916 at 927-928. Thus, in view of the high level of skill in the art, the predictable position of

IgE epitopes among Bet v 1 allergens, and the predictable consequence of mutating amino acid residues within these epitopes (i.e., reduction of IgE binding with retention of native structure) the guidance provided in the specification suffices to describe to one of ordinary skill in the art the full complement of amino acids that can be mutated to arrive at the claimed Bet v 1 allergen mutants.

Certain additional points raised by the Examiner are addressed as follows.

In support of the instant rejection, the Examiner cites in *Ex parte Kubin* (83 U.S.P.Q.2d 1410 (BPAI 2007). In *Kubin*, the Board upheld the rejection of a claim directed to isolated polynucleotides encoding polypeptides that (1) "are at least 80% identical to amino acids 22-221 of SEQ ID NO: 2" (i.e., the amino acid sequence for the extracellular domain of the protein natural killer cell activation inducing ligand ("NAIL") lacking the NAIL signal sequence) and (2) which bind to the glycoprotein CD 48. *Id.* at 1417. The Board found that the Applicant had failed to describe what domains of within amino acids 22-221 of SEQ ID NO: 2 correlated with the function of binding CD 48, and thus the Applicant had not described which NAIL amino acids could be varied and still maintain CD 48 binding. *Id.* The Board found that in the absence of a structure-function correlation, the claim merely defined the invention by function, which was not sufficient to satisfy the written description requirement.

The facts in Kubin differ significantly from the facts of the instant case. In *Kubin*, the Applicant failed to provide any features of amino acids 22-221 of SEQ ID NO: 2 that correlated with binding to CD 48. Nor did the start of the art provide any features of 22-221 of SEQ ID NO: 2 that correlated with binding to CD 48. In the instant case, the three-dimensional structure of Bet v 1 was known when the application was filed, as was the sequence of other Bet v 1 allergens, and the specification discloses that details precisely which amino acids are to be mutated, i.e., solvent-accessible amino acid residues that are conserved among Bet v 1 homologous allergens within the order Fagales, preferably wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400Å of the surface of said naturally-occurring Bet v 1 allergen. Furthermore it was highly predictable that mutations in surface-exposed epitopes would have the desired effect of reducing IgE binding while retaining

native structure of a Bet v 1 mutant. Thus, the state of the art pertaining to the instant invention was significantly more highly advance that the state of the art pertaining to Kubin's invention, the instant application provides significantly more guidance as to which features of the protein in question are important for function, and the effect of mutations on the function of the instantly claimed Bet v 1 mutant allergens (IgE binding) is more predictable than the function of mutations in the NAIL proteins disclosed in Kubin. Thus, the basis of the Board's decision in *Kubin* does not apply to the instant claims.

Lastly, the Examiner characterizes each of the properties called for in the claims as "functional limitations." *See* Office Action at, e.g., page 11. These purported "functional limitations include "reduced specific IgE binding," "occurring in a B-cell epitope," "α-carbon backbone tertiary structure that is preserved," "solvent accessibility of at least 20%," "average root mean square deviation…of less than 2 Å," "within a patch of conserved amino acids connected over at least 400Å of the surface [of naturally occurring Bet v 1]," and "an amino acid sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37."

With two exceptions discussed immediately below, the characterization of these properties as "functional limitations" is mistaken. Each of the other properties is a physical property that flows directly from the (highly conserved) sequence of Bet v 1 allergens. Thus, amino acids with a "solvent accessibility of at least 20" "within a patch of conserved amino acids connected over at least 400Å of the surface [of naturally occurring Bet v 1]" are immediately apparent to one of ordinary skill in the art by simply examining the three dimensional structure of Bet v 1 (or other Bet v 1 allergen modeled on Bet v 1). Identification of "an amino acid sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37" is even more straight forward—one of ordinary skill in the art need only use well known methods to compare Bet v 1 allergen sequences.

With respect to the properties of "α-carbon backbone tertiary structure that is preserved" and "average root mean square deviation…of less than 2 Å," these are features of a

protein that has folded in a native three-dimensional structure, which flows directly from the Bet v 1 sequence (and which is conserved among Bet v 1 allergens). Moreover, as demonstrated by the examples set forth in the specification, Bet v 1 mutants bearing the mutations called for in the claims retain a native structure.

In short, each of the properties discussed above is physical characteristic that is derived directly from the conserved sequences of Bet v 1 allergens. The conserved sequence of Bet v 1 allergens provides a "common partial structural feature" for the claimed Bet v 1 mutants.

Finally, as set forth above, the specification provides ample guidance on Bet v 1 the position of B-cell epitopes on the surface of Bet v 1 allergens and how to predictably make mutations in the amino acids present in these epitopes such that IgE binding is reduced. Accordingly, the specification provides description of the amino acids that can be mutated so as to provide adequate written description for to functional limitations of "reduced specific IgE binding" and "occurring in a B-cell epitope."

For all of the reasons set forth above, the instant specification provides sufficient written description to show the Applicants were in possession of the full scope of the claimed invention when the application was filed. Reconsideration of the claims and withdrawal of all rejections thereof for lack of written description is requested.

III. Conclusion. This application is believed to be in condition for allowance.

Dated: February 6, 2009

Respectfully submitted,

By /Mitchell Bernstein/
Mitchell Bernstein
Registration No.: 46,550
DARBY & DARBY P.C.
P.O. Box 770
Church Street Station
New York, New York 10008-0770
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant